

Eosinophilia-Myalgia Syndrome

THE PRESENCE OF PERIPHERAL EOSINOPHILIA (an absolute eosinophil count of greater than 0.35×10^9 per liter [350 per μ l]) provides a clue to an underlying allergy, parasite infection, the pulmonary infiltrates and eosinophilia syndrome, a neoplasm, vasculitis, an immunodeficiency state, an idiopathic hypereosinophilic syndrome, or a drug reaction. The diagnosis of a drug reaction is usually based on the response to removing the drug and the exclusion of other possible diagnoses, as drug reactions have no pathognomonic clinical or laboratory findings. The association of the eosinophilia-myalgia syndrome (EMS) with the ingestion of the amino acid tryptophan is a striking, newly recognized example of a drug reaction associated with eosinophilia. In response to this association, the Food and Drug Administration banned all over-the-counter sales of tryptophan in December 1989.

The current surveillance definition of EMS used by the Centers for Disease Control (CDC) requires the fulfillment of three criteria: an eosinophil count of greater than 1×10^9 cells per liter (1,000 cells per μ l), incapacitating myalgias, and the exclusion of other infectious and neoplastic causes. In addition to the prominent muscle involvement (myalgias and muscle tenderness), other organs involved in EMS include the skin (edema of the skin, transient maculopapular or urticarial rash and late morphealike lesions), lungs (dyspnea, cough, hypersensitivity pneumonitis), heart (palpitations, myocarditis), joints (arthralgias), and peripheral nerves (paresthesia). Although creatine kinase levels are usually normal, aldolase levels are frequently elevated, and a muscle biopsy specimen shows perivascular infiltrates of eosinophils and mononuclear cells. Patients with EMS have degranulated eosinophils in affected tissues, widespread activation of collagen gene expression in dermal fibroblasts, and increased tryptophan metabolism by way of the kynurenine pathway.

Available in the United States since about 1974 as a dietary supplement without prescription, tryptophan has been a popular remedy for insomnia, the premenstrual syndrome, depression, and loss of weight. Average patient doses of tryptophan range from 1 to 5 grams per day. In comparison, single servings of meat, fish, poultry, and some cheeses contain more than 200 mg of tryptophan. Tryptophan is metabolized by way of hydroxytryptophan to serotonin or by an alternative pathway to kynurenine. Because tryptophan is an essential amino acid, the presence of a contaminant or impurity in tryptophan products has been postulated to be responsible for the syndrome. In Minnesota, an analysis of the epidemiology of EMS has revealed that the outbreak of EMS was associated with the consumption of tryptophan manufactured by one of six manufacturers providing tryptophan to US consumers before December 1989. Even though the purity of tryptophan in the company's manufacturing process was at least 99.6%, a trace contaminant formed after a chemical reaction between two tryptophan molecules and acetaldehyde (1,1'-ethylidenebis [tryptophan]) has been associated with the risk of EMS developing.

At least 19 deaths and more than 1,400 cases of severe inflammatory disease due to EMS have been reported to the CDC. While the current CDC surveillance criteria for the diagnosis of EMS may exclude patients with milder forms of the syndrome, caution should still be exercised in diagnosing EMS in patients without eosinophilia because various rheumatic diseases, including fibrositis, polymyalgia rheu-

matica, and systemic sclerosis, may produce similar clinical manifestations. Therefore, the diagnosis of EMS in patients with milder myalgias, lower eosinophil counts, or other features suggestive of EMS requires clinical judgment and the appropriate weighing of all available clinical, laboratory, and, where indicated, muscle biopsy information. Because the only clear-cut recommendation for therapy (to stop ingesting tryptophan) has already been made, the use and the duration of other therapies, such as glucocorticoids, needs to be tailored to each patient, depending on the severity of the disease and risk-benefit considerations.

Although further studies may provide important insights into the cellular mechanisms of action of the postulated trace contaminant responsible for EMS, the identification of tryptophan as the etiologic agent associated with the development of EMS and its prompt removal from the over-the-counter market has prevented EMS from becoming an even greater public health concern.

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Asthma Without Wheezing

ASTHMA IS A DISORDER characterized clinically by episodes of wheezing, dyspnea, cough, and chest tightness. Spirometry shows reversible airways obstruction, but asthma may present with dry cough as its sole manifestation. This form of asthma has been variously termed "hidden," "atypical," "variant," or "cough-type" asthma. It appears to be a distinct disorder and is characterized by a dry, repetitive cough occurring during waking as well as sleeping hours that may be exacerbated by respiratory viral infections, exercise, and cold air. Frequently members of the immediate family have a history of allergy. Although found in all ages, atypical asthma is thought to be among the most common causes of chronic cough in childhood.

The cough of asthma is unresponsive to antitussives, antibiotics, and antihistamines, but it usually responds to a course of bronchodilators or corticosteroids. Routine spirometry may be normal. The diagnosis can be confirmed by a positive methacholine or exercise challenge test. The bronchial hyperresponsiveness evidenced by these tests is mostly reversed by the use of bronchodilators. In time, many patients have progression to typical asthma. In the differential diagnosis, other sources of cough should be considered, including the central nervous system and the pulmonary interstitium. Conditions such as pertussis, psychogenic cough, cystic fibrosis, sinusitis, and drug reactions are usually readily excluded.

One reason cited for cough without wheezing is that cough receptors are separate from the irritant receptors, which are responsible for wheezing. In one study the predominance of cough in a group of patients with asthma was attributed to cough receptors stimulated in the trachea and